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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHOI, Hoo-Kyun [KR/US]; 1280 McDivitt Drive, Blue Bell, PA 19422 (US). WILLIAMS, James, B. [US/US]; 2259 Warner Road, Lansdale, PA 19446 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: POUR-ON FORMULATIONS CONTAININNG POLYMERIC MATERIAL, GLYCOLS AND GLYCERIDES

(57) Abstract

There is disclosed a topical formulation containing glycols, glycerides, or their derivatives, an avermectin compound (active ingredient) and optionally a polymeric material which has been discovered to provide superior efficacy against endoparasites and ectoparasites when compared to conventional formulations and to maintain the concentration of the active compound in the milk of dairy animals below a safe concentration for human consumption. The formulation contains the avermectin active ingredient and at least 50 % of the glycol or glyceride or polymeric material.

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TITLE OF THE INVENTION

POUR-ON FORMULATIONS CONTAINING POLYMERIC MATERIAL, GLYCOLS AND GLYCERIDES

BACKGROUND OF THE INVENTION

The avermectin series of compounds are potent anthelmintic and antiparasitic agents against internal and external parasites. The natural product avermectins are disclosed in U.S. 4,310,519 to Albers-Schonberg et al., and the 22,23-dihydroavermectin compounds are disclosed in Chabala et al., U.S. 4,199,569. Administration of the avermectin compounds occur orally, parenterally or topically.

However, the conventional topical formulations do not provide acceptable efficacy against ectoparasites, especially against Chorioptes, fleas and ticks. Often times these formulations fail due to the lack of extended efficacy. The animals are readily reinfested by fleas, ticks and the like after treatment with the above-noted formulations simply by returning to a flea infested environment. Further, topical formulations of currently available medicinal agents have not demonstrated efficacy against endoparasites, such as heartworms and nematodes.

It is known in the pet care industry that sustained release of an insecticide is obtained by incorporation of the insecticide into a polymeric system. However, conventional polymer based formulations rely on the vaporization of the active compounds, which means this type of system may not be used for non-evaporable drugs. See U.S. Pat. Nos. 3,852,416 and 4,172,904. Additionally, conventional formulations of current medicinal agents require a withdrawal period of a few weeks after application of the active compound before any milk can be withdrawn from dairy animals for human consumption.

SUMMARY OF THE INVENTION

This invention is concerned with avermectin topical pour-on formulations which effectively eliminate both ectoparasites,

especially Chorioptes, fleas and ticks, and endoparasites, especially heartworms and nematodes, of animals such as cattle, swine, etc for an extended period up to a full four weeks, particularly household pets such as cats and dogs.. The instant formulations also unexpectedly provides a zero milk withdrawal time for topically applied antiparasitic agents with regard to dairy animals. The formulations are prepared using solvents such as water, alcohols such as ethanol, methanol, isopropanol and the like, propylene glycol esters, glycerides, or their derivatives as the carrier.

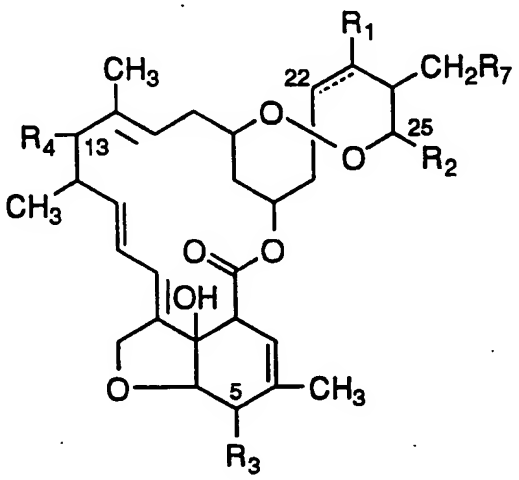
The formulations can contain in addition to the active avermectin ingredient and solvent, a polymer such as polyvinylpyrrolidone. The drug is bound to the skin with the aid of the polymer which remains on the skin surface after the solvents have evaporated following application. Thus it is an object of this invention to describe such ectoparasitic and endoparasitic efficacy. Another object is to describe the avermectin compounds which may be employed in the formulation. A still further object is to describe how the concentration of the active compound in the milk of dairy animals is maintained below a concentration level that provides for a zero withdrawal period for human consumption. A still further object is to describe how extended efficacy against ticks, fleas and heartworms is obtained. Additional objects will become apparent after a reading of the following description.

DESCRIPTION OF THE INVENTION

This invention consists of a topical formulation of a glyceride, glycol, or a derivative thereof and an avermectin compound which has been found to effectively eliminate both ectoparasites and endoparasites.The formulation can optionally contain in addition to the glyceride, glycol or derivative thereof and avermectin, an antioxidant such as BHA, BHT and the like, additives such as Crodamol CAP, glycerol formal, Tween 80 and the like, a solvent mixture of water and/or solvents with relative high vapor pressure such as ethanol,

methanol, isopropanol and the like, and a polymeric material such as polyvinyl pyrrolidone, polyvinyl alcohol and the like.

The avermectin compounds used in the instant formulations have the following general structure:



where the broken line indicates a single or a double bond at the 22,23-positions;

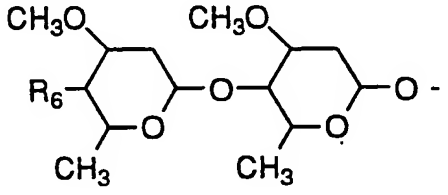
R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 8 carbon atoms;

R_3 is hydroxy, methoxy or = NOR_5 where R_5 is hydrogen or lower alkyl;

R_7 is hydrogen, hydroxy, or lower alkyl; and

R_4 is hydrogen, hydroxy, poly C(1-6) alkoxy or



where R_6 is hydroxy, amino, mono-or di-C_1 to C_6 alkylamino or C_1 to C_6 alkanoylamino.

The term "loweralkyl" when used in the instant application is intended to represent those alkyl groups either straight or branched chain which have from 1-5 carbon atoms. Examples of such alkyl groups are methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, pentyl, and the like.

The term "loweralkanoyl" is intended to include those alkanoyl groups containing from one to five carbon atoms in either a straight or branched chain. Examples of such alkanoyl groups are formyl, acetyl, propenyl, butyryl, valeryl, and the like.

The term "halogen" is intended to include those halogen atoms fluorine, chlorine, bromine and iodine.

The term "polyalkoxy" is intended to include methoxymethoxy, 2-methoxyethoxy, (2-methoxyethoxy)-methoxy, [2-(2-methoxyethoxy)ethoxy]methoxy; and the like.

A related family of natural products also useful in the present invention is known as the milbemycins. The milbemycins have the same macrocyclic ring structures as the avermectins but have no substitution at position 13 (R_4 = hydrogen) and have a methyl or ethyl group at position 25 (R_2 = methyl or ethyl rather than isopropyl or sec-butyl as in the avermectins). The milbemycins and the fermentation conditions used to prepare them are described in U.S. Pat. No. 3,950,360. Closely related 13-deoxyavermectin aglycones are prepared by chemical modification of the natural avermectins and have been described in U.S. Pat. No. 4,173,571.

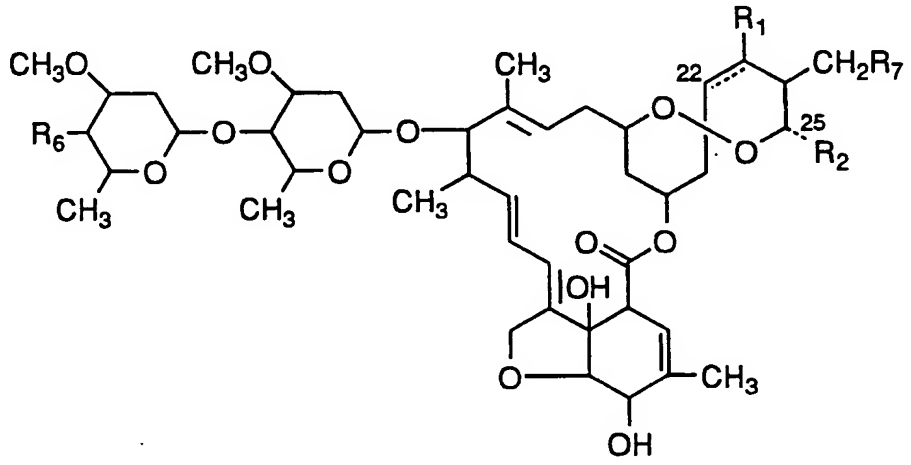
One preferred embodiment (E1) of this invention consists of a topical pour-on formulation of a gylceride, glycol, or a derivative thereof as a carrier and an avermectin compound which has been found to effectively eliminate both ectoparasites, especially Chorioptes, and endoparasites, while simultaneously maintaining the concentration of the active compound in the milk of dairy animals below an adequate concentration period for human consumption to provide a zero milk

withdrawal time for topically applied endectocides [milk concentration of 4"-acetylamino-4"-deoxyavermectin B1 (L-653,648) for zero milk withdrawal is 48 ng/ml] .

The carriers are oleyl alcohol, propylene glycol and its esters such as propylene dicaprylate/dicaprate, propylene glycol laurate, and the like, glycol ethers such as diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol diethyl ether and the like, and glycerides such as PEG-6 caprylic/capric triglyceride, caprylic/capric diglyceryl succinate, polyglycolysed glycerides, and the like, preferrably propylene caprylate/caprate or caprylate caprate glyceride, and is available under such brand names as Miglyol 810, 812, 818, 829 and 840, Softigen and Labrasol®. The (/) in propylene dicaprylate/dicaprate and PEG-6 caprylic/capric triglycerides indicates a mixture of the two components in a ratio of 65-80/15-30.

The above carriers impart to the formulation good penetration and spreadability of the active compound even at cold temperatures.

The preferred avermectin compounds of E1 have the following structural formula:



wherein the broken line represents a single bond; R_1 is hydrogen; R_2 is isopropyl of sec-butyl; R_6 is hydroxy, amino, mono-or di-C_1 to C_6

alkyl-amino or C_1 to C_6 alkanoylamino; and R_7 is hydrogen, hydroxy, or loweralkyl.

Examples of preferred compounds of the instant E1 formulation are:

4"-keto avermectin B1;
4"-keto avermectin B2;
4"-keto-22,23-dihydro avermectin B1;
4"-keto-22,23-dihydro avermectin B2;
4"-deoxy-4"-amino avermectin B1;
4"-deoxy-4"-amino avermectin B2;
4"-deoxy-4"-amino-22,23-dihydro avermectin B1;
4"-deoxy-4"-amino-22,23-dihydro avermectin B2;
4"-deoxy-4"-acetylamino avermectin B1;
4"-deoxy-4"-acetylamino avermectin B2;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-dimethylamino avermectin B1;
4"-deoxy-4"-dimethylamino avermectin B2;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B1;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B2.

The "b" compounds, those with a 25-iso-propyl group, are not necessarily separated from the corresponding "a" compound with a 25-sec-butyl group and the compounds are generally isolated as

mixtures of the two compounds, consisting of at least 80% of the sec-butyl compound and no more than 20% of the iso-propyl compound. Thus references in the instant application to "a" compounds such as Bla, Ala, and the like, are construed to actually contain a certain proportion of the corresponding "b" compound. Alternatively, this representation of a mixture is sometimes done by referring to the Bl or B2 compounds or by separating the "a" compound from the "b" compound by a slash (/) such as Bla/Blb, B2a/B2b and the like. Additionally, the products of synthetic procedures such as racemization or epimerization, procedures known to those skilled in the art, can be a mixture of stereoisomers. In particular, the stereoisomers at the 13- and 23-positions may be oriented either α- or β- representing such groups being below or above the general plane of the molecule, respectively. In each case, and at other positions in the molecule, both the α- and β- configurations are intended to be included within the ambit of this invention.

In the topical forms of the avermectin formulation it has not been possible to provide a formulation which provides an acceptable efficacy against ectoparasites, especially Chorioptes. Additionally, currently available topical formulations do not provide a zero milk withdrawal time with the application of endectocides which thus precludes the use of such compounds on milk producing animals.

E1 of the instant invention gives the advantages of a pour-on topical formulation which provides the animal with effective treatment and protection against endoparasites and ectoparasites, especially Chorioptes and at the same time maintains the concentration of the active compound in the milk of dairy animals below a safe concentration for human consumption. Additional advantages of this invention are that the formulation is non-flammable, it is not readily washable by rain, it has good spreadability and cold temperature usage and has good compatibility with currently available dosing devices.

E1 can contain the avermectin compound and the glycol or glyceride carrier as the only ingredients. The formulations will generally be prepared to administer a safe and effective amount from 0.005 to 10% by weight of the avermectin component, most preferrably

from 0.01 to 5% by weight. Most preferably a formulation containing about 0.5% of the avermectin is employed. At a preferred dose volume of about 5 ml to treat 50 kg of animal body weight the formulation contains from about 1.0 to 50 mg of avermectin compound per ml of solution. The glycol or glyceride carrier is added to the formulation from about 40 to 100% (q.s.v/v).

The most preferred formulation for E1 contains in addition to the glycol, glyceride, or derivatives thereof and avermectin compound, an antioxidant such as propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene) monothioglycerol and the like, preferrably BHT. The anti-oxidants are generally added to the formulation at rates of from 0.005 to 1.0% (w/v). Additives such as Crodamol CAP, glycerol formal, Tween 80 propylene glycol and the like, preferrably Crodamol CAP, may also be used. The additives are generally added to the formulation at volumes of up to 60% of the volume of glycol or glyceride carrier, preferrably up to 40% of the volume of carrier.

E1 is prepared by dissolving the avermectin compound in approximately 50-100% of the intended volume of the above mentioned carriers and then adjusting the volume to 100% by the addition of the final volume of the carrier or additive. The anti-oxidant and additive may be combined with the above mentioned carriers prior to mixing the avermectin or added as the final volume of solvent.

The following example is provided in order that the E1 emobodiment of the invention might be more fully understood. It is not to be construed as a limitation of the invention.

EXAMPLE OF E1 OF THE INVENTION

The formulations of this invention depend upon the particular avermectin compound and treatment. The avermectin is dissolved in approximately 50% of the glycol or glyceride carrier. When dissolved, the antioxidant and/or additive are optionally added and the volume adjusted to 100% with the final volume of glycol or glyceride carrier. The solution is mixed until it becomes homogeneous. Generally, mixing at room temperature (15-25°C) is adequate however,

if necessary, warming up to 50°C may be helpful. The following are nonlimiting examples of the composition of the present invention, which are conventionally formulated by mixing all components as stated above.

Composition I	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Crodamol CAP	10.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v
Composition II	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Miglyol 840 (q.s.)	100.0 % v/v
Composition III	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Isopropyl Myristate	10.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v
Composition IV	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
Triacetin	50.0 % v/v
Miglyol 840 (q.s.)	100.0 % v/v

Composition V	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
Softigen 767	65.0 % v/v
Miglyol 840	25.0 % v/v
Ethanol (q.s.)	100.0 % v/v

Composition VI	
4"-acetylamino-4"-deoxyavermectin	0.5 % w/v
Softigen 767	65.0 % v/v
Isopropanol (q.s.)	100.0 % v/v

Composition VII	
4"-acetylamino-4"-deoxyavermectin B1	0.5 % w/v
BHT	0.01% w/v
Dowanol DB (q.s.)	100.00% v/v

Crodamol CAP is a tradename mixture of isopropyl myristate, cetyl octanoate and stearyl octanoate and Dowanol DB is a tradename for diethylene glycol butyl ether.

E1 EXAMPLE II

The data below are results indicating the avermectin concentration (ng/ml) in the milk of lactating cows after topical application with some of the above formulations and that the avermectin concentration is maintained below 48 ng/ml which is the milk concentration of avermectin required for a zero milk withdrawal.

4"-ACETYLAMINO-4"-DEOXYAVERMECTIN B1
CONCENTRATIONS (ng/mL) IN MILK
OF LACTATING COWS DOSED TOPICALLY

TREATMENT A: MIGLYOL 840/BHT/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5950	0.0	1.5	5.0	6.4	9.5	8.7	8.1	6.3
5931	0.0	6.0	23.2	13.0	7.1	4.2	2.5	1.7
5932	0.0	3.4	4.8	3.4	3.1	2.0	1.6	3.4
5938	0.0	5.6	15.5	9.6	8.5	4.5	3.7	3.1
MEAN	0.0	4.1	12.1	8.1	7.1	4.9	4.0	3.6
STD. DEV.		2.1	8.9	4.1	2.8	2.8	2.9	1.9

TREATMENT B: TRIACETIN/MIGLYOL 840 (50/50)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5946	0.0	1.2	2.9	4.0	5.0	4.7	4.1	2.9
5949	0.0	2.7	13.3	11.4	8.6	5.3	3.5	2.8
5929	0.0	1.3	2.8	4.1	5.8	5.7	4.2	3.0
5928	0.0	4.9	14.6	9.4	5.4	3.1	2.0	1.4
MEAN	0.0	2.5	8.4	7.2	6.2	4.7	3.5	2.5
STD. DEV.		1.7	6.4	3.8	1.6	1.1	1.0	0.8

TREATMENT C: SOFTIGEN 767/MIGLYOL 840 (70/30)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5948	0.0	1.1	4.5	6.4	6.6	7.1	5.4	3.8
5930	0.0	1.4	3.8	3.9	5.8	9.0	7.6	4.9
5927	0.0	2.7	6.0	7.0	7.6	5.5	4.6	3.7
5934	0.0	1.9	4.7	10.6	15.0	8.3	4.9	3.2
MEAN	0.0	1.8	4.8	7.0	8.8	7.5	5.6	3.9
STD. DEV.		0.7	0.9	3.9	4.2	1.5	1.4	0.7

TREATMENT D: Miglyol/Crodamol CAP (90/10)-500 µg/Kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
6384	0.0	2.1	4.8	6.8	7.6	5.7	5.4	3.8
6385	0.0	7.3	7.1	6.1	4.8	3.3	2.7	2.3
6379	0.0	10.0	10.6	7.8	5.4	2.9	1.9	1.7
6386	0.0	2.7	6.0	6.0	5.8	4.1	5.4	5.2
6377	0.0	5.2	9.7	8.7	9.8	4.8	2.9	2.5
6382	0.0	7.7	15.5	11.8	8.7	4.7	3.3	2.3
MEAN	0.0	5.8	9.0	7.9	7.0	4.3	3.6	3.0
STD. DEV.		3.1	3.9	2.2	2.0	1.0	1.5	1.3

TREATMENT E: Miglyol/Crodamol CAP (90/10)-250 µg/Kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
6389	0.0	1.2	2.7	2.8	2.6	1.9	1.7	1.4
6381	0.0	1.0	1.6	1.8	2.8	2.5	2.6	2.0
6380	0.0	2.8	5.5	4.4	3.5	2.0	1.5	0.0
6378	0.0	2.4	4.8	4.0	2.9	1.6	1.1	0.0
6376	0.0	1.8	4.2	4.3	4.3	3.1	2.4	1.9
6388	0.0	0.0	1.3	1.7	2.8	2.3	2.0	1.9
MEAN	0.0	1.5	3.4	3.2	3.2	2.2	1.9	1.2
STD. DEV.		1.0	1.7	1.2	0.6	0.5	0.6	1.0

TREATMENT F: TRIACETIN/MIGLYOL 840 (50/50)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5977	0.0	1.4	6.8	6.9	4.3	3.4	3.0	2.2
5976	0.0	2.1	10.8	13.8	5.7	5.6	2.9	1.8
MEAN	0.0	1.8	8.8	10.4	5.0	4.5	3.0	2.0
STD. DEV.		0.5	2.8	4.9	1.0	1.6	0.0	0.3

TREATMENT :G IPA/SOFTIGEN 767 (40/60)/500 ug/kg

ANIMAL #	DAY POST DOSE							
	0	1	2	3	4	5	6	7
5984	0.0	0.0	0.0	0.6	0.6	0.7	1.0	1.6
5980	0.0	0.5	0.8	1.6	1.3	2.9	2.3	2.8
5987	0.0	0.0	0.5	0.9	3.1	6.3	4.6	5.0
5982	0.0	0.0	2.0	3.8	3.8	3.5	2.2	1.6
MEAN	0.0	0.0	0.8	1.7	2.2	3.4	2.5	2.8
STD. DEV.		0.0	0.9	1.5	1.5	2.3	1.5	1.6

NOTE: Samples with 4"-acetylamino-4"-deoxyavermectin B1 concentrations equal to or less than 0.4 ng/ml are reported as 0 ng/ml:

E1 EXAMPLE III

Efficacy trials with Chorioptes and key endoparasites were conducted to evaluate some of the above formulations. For each trial evaluating Chorioptes, four cattle were infested with *Chorioptes bovis* on Day -1 and treatment was given on Day 0. Respecting the trials evaluating endoparasites, the animals were challenged with Oesophagostamum, Trichuris and Dictyocaulus 17, 7, and 7 days before treatment with the formulation. The results are below.

CHORIOPTES MITE COUNTS

An. No.	Day -1	Day 7	Day 14	Day 21	Day 27	Day 35
Trt. 1 - Untreated Control						
H215	32	3	0	10	0	0
H208	6	19	15	3	4	17
H229	708	5024	2546	601[a]	11477[b]	6835
H233	511	875	1430	889[a]	1432[b]	1339
Trt. 2 - 4"-aa-4" deoxy in Miglyol 840/Crodamol CAP/BHT at 500 mcg/kg						
H224	22	1	79	2	0	0
H223	17	0	0	0	0	0
H234	2018	1007	895	0[a]	0[b]	0
H230	378	265	2	5[a]	0[b]	150
Trt. 3 - 4"-aa-4" deoxy in Miglyol 840/BHT at 500 mcg/kg						
H226	182	3	0	1	0	0
H218	3	0	0	0	0	0
H228	1644	659	16	0[a]	0[b]	0
H231	233	358	603	133[a]	89[b]	5

[a] Day 20

[b] Day 28

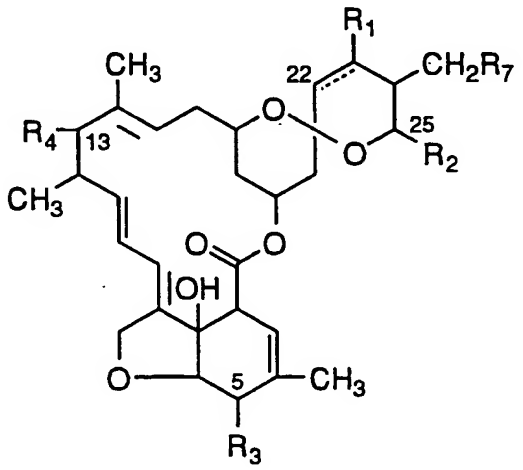
4"-aa-4" deoxy = 4"-acetylamino-4"-deoxy avermectin B1

4"-aa-4" deoxy Nematode Counts
Total Counts based on 10% aliquots
(*Dictyocaulus* counts are total counts)

Animal Number	*Oesophagost* spp. Adult	*Oesophagost* spp. L4	*Trichuris* spp. Adult	*Dictyocaulus* spp.
Trt. 1 - Untreated Control				
2477	0	0	20	3
2374	50	0	0	0
2259	0	0	50	17
41	240	0	80	14
Trt. 2 - 4"-aa-4" deoxy in Miglyol 840 Crodamol CAP/BHT (0.5%/q.s./10%/0.01% at 500 mcg/kg				
2456	0	0	0	0
2478	0	0	0	0
5	0	0	0	0
2254	0	0	0	0
Trt. 3 - 4"-aa-4" deoxy in Miglyol 840 BHT (0.5%/q.s./0.01%) at 500 mcg/kg				
2510	0	0	0	0
2358	0	0	0	0
40	0	0	0	0
2258	0	0	0	0
Trt. 4 - 4"-aa-4" deoxy in Miglyol 840/Lauroglycol/BHT (0.5%/q.s./10%/0.01%) at 500 mcg/kg				
2528	0	0	0	0
2443	0	0	0	0
44	0	0	0	0
2298	0	0	0	0

Another preferred embodiment (E2) of the instant formulation consists of a topical pour-on formulation of a solvent mixture of water and/or solvents with relative high vapor pressure such as ethanol, methanol, isopropanol, acetone, and the like, most preferrably ethanol, a polymeric material such as polyvinyl pyrrolidone, polyvinyl alcohol, cellulose derivatives such as methyl cellulose, ethyl cellulose, carboxy methyl cellulose, and hydroxyethyl cellulose, and the like, most preferrably polyvinyl pyrrolidone (MW from about 20,000 to 65,000, preferrably about 45,000), skin or hair subtantantive protein derivatives such as hydrolyzed wheat protein, hydrolyzed animal protein, gelatin derivatives, collagen derivatives, and the like, hydroalcoholic soluble copolymers such as acrylates/t-octylpropenamide copolymer and the like, and cationic quaternary amine salts and the like, which has been found to extended the efficacy of the formulation for up to a full four weeks. The polymeric material helps to keep the drug at the skin level longer by remaining on the skin surface after the solvents have evaporated following application. The remaining avermectin and polymer does not change the appearance of the animal's hair coat and the avermectin is released by diffusion and/or erosion of the polymer.

The preferred avermectin compounds of E2 have the following structural formula:



wherein R_1, R_2, and R_3 are as described above, and R_4 is hydrogen, hydroxy, or polyalkoxy, and the broken line indicates a single or double bond at the 22,23-position, provided that R2 is hydroxy only when the broken line indicates a single bond.

Examples of preferred compounds of the instant invention are:

4"-keto avermectin Bl;
4"-keto avermectin B2;
4"-keto-22,23-dihydro avermectin Bl;
4"-keto-22,23-dihydro avermectin B2;
4"-deoxy-4"-amino avermectin Bl;
4"-deoxy-4"-amino avermectin B2;
4"-deoxy-4"-amino-22,23-dihydro avermectin Bl;
4"-deoxy-4"-acetylamino avermectin Bl;
4"-deoxy-4"-acetylamino avermectin B2;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin Bl;
4"-deoxy-4"-acetylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-dimethylamino avermectin Bl;
4"-deoxy-4"-dimethylamino avermectin B2;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B1;
4"-deoxy-4"-dimethylamino-22,23-dihydro avermectin B2;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro avermectin Bl;
4"-deoxy-4"-p-chloro benzenesulfonylamino-22,23-dihydro-13-O-[(2-methoxyethoxy)methyl] avermectin Bl aglycone (hereinafter referred to as 13-O-MEM AVM);
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin Bl;
4"-deoxy-4"-(2-methylbenzenesulfonylamino)-avermectin B2
13-epi-O-(methoxymethyl)-22,23-dihydro avermectin B1 aglycone (hereinafter referred to as 13-O-MOM AVM).

The most preferred compound is 22,23-dihydro-13-O-[(2-methoxyethoxy)methyl] avermectin B1 aglycone (hereinafter referred to as 13-O-MEM AVM).

In the topical forms of the avermectin formulation it has not been possible to provide a formulation which provides superior extended efficacy against ectoparasites, especially fleas and ticks. Additionally, currently available topical formulations do not provide adequate efficacy against endoparasites, especially heartworms and nematodes.

The E2 embodiment of the instant formulation gives the advantages of a pour-on topical formulation which provides the animal with extended effective treatment and protection against endoparasites and ectoparasites, especially fleas, ticks, mange mites, hookworms, ascarids, and heartworms. Additional advantages of this invention are that the formulation is not readily dislodgeable by petting the animals, it has good spreadability and cold temperature usage.

The E2 embodiment of the instant formulation can contain the avermectin compound, alcohol, water and the polymer as the only ingredients. The formulations will benerally be prepared to administered the avermectin from about 0.005 by weight to about 30% of the total composition, preferrably from 0.1 to 10% by weight and most preferrably about 5% by weight of the active ingredient. At a preferred dose of about 0.5 to 50 mg/kg the formulation is applied at a dose volume of 0.05 to 4.0 ml/kg body weight. The polymer is present in the compositions of the present invention in amounts ranging from about 0% to 20% w/v and preferrably from about 0.5 to 10% w/v by weight of the total composition and up to 95% by volume of alcohol, q.s. to 100% with water.

The preferred E2 embodiment contains in addition to the polymer, alcohol, water and avermectin compound, additional ingredients such as antioxidants and the glycol, glycerides, glycol ethers, and the derivatives thereof mentioned above. The anti-oxidants are generally added to the formulation at rates of from 0.005 to 1.0% (w/v)

and can be propyl gallate, BHA (butylated hydroxy anisole), BHT (butylated hydroxy toluene), monothioglycerol and the like, preferrably BHT.

The E2 formulation is prepared by dissolving the avermectin compound in the intended volume of alcohol. The anti-oxidant and one of the polymeric materials listed above are then dissolved in the alcohol/avermectin mixture. The volume is then adjusted to 100% by the addition of the final volume of water, with the solution being mixed until it becomes homogeneous. Alternatively, either the BHT or the polymer, or both can be added prior to the addition of the avermectin compound.

The following example is provided in order that the E2 emobodiment of the invention might be more fully understood. It is not to be construed as a limitation of the invention.

EXAMPLE OF E2 OF THE INVENTION

The E2 formulations of this invention which are employed depend upon the particular avermectin compound and treatment. To test the effective killing power of the E2 formulations against fleas and ticks, the following compositions were prepared:

Composition VIII

13-O-MEM AVM	0.3 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Cremophor RH-40	1.0 % w/v
Anhyd. (Denatured) Ethanol	40.0 % v/v
Softigen 767	20.0 % v/v
Water (q.s.)	100.0 % v/v

Composition IX

13-O-MEM AVM	0.3 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	75.0 % v/v
Water (q.s.)	100.0 % v/v

BHT	0.01% w/v

Composition X

13-O-MOM AVM	5.0 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
BHT	0.01% w/v

Composition XI

13-O-MEM AVM	0.6 % w/v
polyvinyl pyrrolidone	5.0 % w/v
Anhydrous Ethanol	75.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XII

13-O-MEM AVM	0.6 % w/v
hydrolyzed wheat protein	3.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XIII

13-O-MEM AVM	0.6 % w/v
Ethocel	2.0 % w/v
Anhydrous Ethanol	90.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

Composition XIV

13-O-MEM AVM	0.6 % w/v
polyvinyl pyrrolidine	5.0 % w/v
Anhydrous Ethanol	80.0 % v/v

Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v
Miglyol	0.5 % v/v

Composition XV

13-O-MEM AVM	0.6 % w/v
acrylates/t-octylpropenamide copoly	1.0 % w/v
polyvinyl pyrrolidone	2.0 % w/v
Anhydrous Ethanol	80.0 % v/v
Water (q.s.)	100.0 % v/v
Vitamin E	0.02% v/v

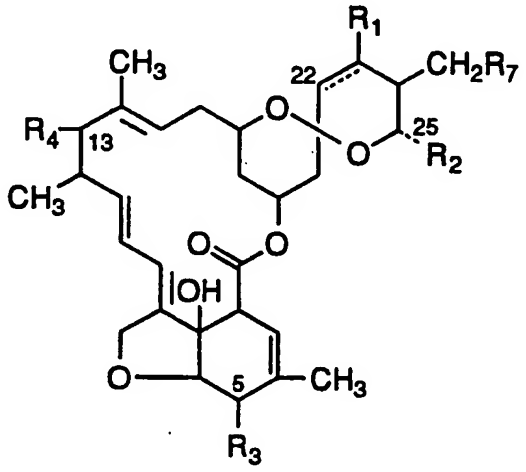
Softigen 767 is a tradename for PEG-6 caprylic/caprate glyceride, Cremophor RH-40 is a tradename for a mixture of glycerol polyethylene and glycol oxysteasrate, and Ethocel is a tradename for ethyl cellulose.

Composition X above was topically applied in multiple locations, typically 2 to 6 points spaced equidistant between the back of the neck and the head of the tail of a flea infested dog. Counts were made by combing the hair, removing and counting the live parasites on the dog at a specified time. The observed flea kills varying the amount of 13-O-MEM AVM, is given in Table No. 1 below, where 60 dogs were allocated to four treatment groups. The dogs were infested with 100 unfed, adult fleas at times indicated by the down arrow ( ), which is equivalent to three days before a flea count is conducted. Treatment was applied on day zero. Table No. 2 summarizes the results of a similar test evaluating the efficacy of the composition, containing 13-O-MEM AVE (termed 2-MEM) in various vehicles, in the treatment of ticks.

The instant formulations can be topically administered to warm blooded animals to provide long acting treatment and protection against endoparasites and ectoparasites either locally at the site of infestation or at multiple points, typically 2 to 6 points (multiple-point-application) along the back of domesticated animals and household pets such as cattle, sheep, cats, dogs and the like.

WHAT IS CLAIMED IS:

1. A topical formulation consisting of from about 40 to 100% q.s., v/v of a glycol, glyceride, or derivative thereof carrier, from about 0% to from about 20% of a polymeric material and from 0.005 to 10% w/v of an avermectin compound having the formula:



where the broken line indicates a single or a double bond at the 22,23-positions;

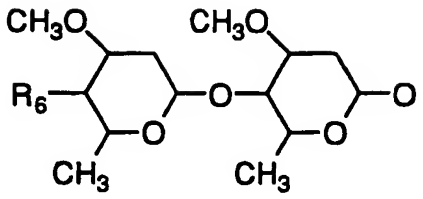
R_1 is hydrogen or hydroxy provided that R_1 is present only when the broken line indicates a single bond;

R_2 is alkyl of from 1 to 6 carbon atoms or alkenyl of from 3 to 6 carbon atoms or cycloalkyl of from 3 to 6 carbon atoms;

R_3 is hydroxy, methoxy or $=NOR_5$ where R_5 is hydrogen or lower alkyl;

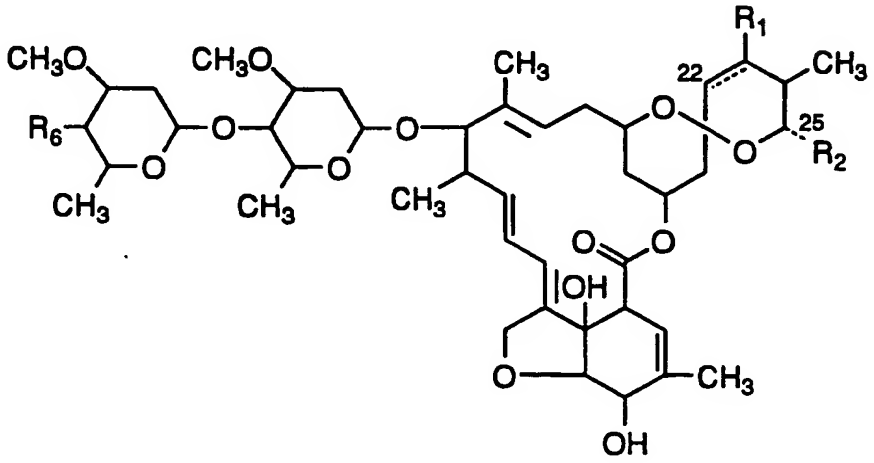
R_7 is hydrogen, hydroxy or loweralkyl; and

R_4 is hydrogen, hydroxy, C(1-6) polyalkoxy or



where R_6 is hydroxy, amino, mono- or di-C_1-C_6 alkylamino or C_1-C_6 alkanoylamino.

2. The formulation of Claim 1 wherein R_4 is



wherein R_1, R_2, and R_6 are stated as in Claim 1.

3. The formulation of Claim 1 which contains from 0.01 to 5% w/v of the avermectin compound.

4. The formulation of Claim 1 wherein the carrier is oleyl alcohol, propylene glycol, propylene dicaprylate/dicaprate, propylene glycol laurate, diethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol diethyl ether, PEG-6 caprylic/capric glyceride, acetylated monoglyceride, triacetin,

caprylic/capric triglyceride, caprylic/capricdiglyceryl succinate, or polyglycolysed glycerides.

5. The formulation of Claim 4 wherein the carrier is propylene dicaprylate/dicaprate, or caprylate/caprate glyceride.

6. The formulation of Claim 1 which contains in addition to the carrier and the avermectin compound, an anti-oxidant from 0.005 to 1.0% w/v.

7. The formulation of Claim 6 wherein the antioxidant is n-propyl fallate, BHA, BHT, or monothioglycerol.

8. The formulation of Claim 7 wherein the antioxidant is BHT.

9. The formulation of Claim 1 which optionally contains an additive at up to 60% v/v, the additive being Crodamol Cap, glycerol formal, Tween 80, or propylene glycol.

10. The formulation of Claim 1 consisting of 100% q.s., v/v propylene dicaprylate/dicaprate or caprylate/caprate glyceride, from about 0.005 to 0.05% w/v BHT and from about 0.01 to 5% w/v of 4"-acetylamino-4"-deoxyavermectin B1.

11. The formulation of Claim 10 consisting 0.5% w/v of 4"-acetylamino-4"-deoxyavermectin B1, and 0.01% w/v BHT.

12. The formulation of claim 1 wherein the glycol derivative is from about 1% to from about 95% v/v of an alcohol and which contains from about 0.01 to from about 20% w/v of the polymeric material with 100% v/v obtained with addition of water.

13. The formulation of claim 12 wherein R4 is hydrogen, hydroxy or polyalkoxy.

14. The formulation of claim 12 which contains from 0.1 to 5.0% w/v of the avermectin compound and 5.0 to 10% of the polymeric material and wherein R4 of the avermectin compound is $CH_3OCH_2CH_2OCH_2O$.

15. The formulation of claim 12 wherein the polymeric material is selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, methyl cellulose, ethyl cellulose, carboxy methyl cellulose, hydroxyethyl cellulose, hydrolyzed wheat protein, hydrolyzed animal protein, gelatin derivatives, collagen derivatives, acrylates/t-octylpropenamide copolymer and cationic quaternary amine salts and the alcohol is selected from the group consisting of ethanol, methanol, isopropanol, and butanol.

16. The formulation of claim 15 wherein the polymeric material is polyvinyl pyrrolidone and the alcohol is ethanol.

17. The formulation of claim 16 wherein the polyvinyl pyrrolidone has a molecular weight of about 20,000 to about 65,000.

18. The formulation of claim 17 wherein the polyvinyl pyrrolidone has a molecular weight of 45,000.

19. The formulation of claim 12 which optionally contains an anti-oxidant selected from the group consisting of n-propyl gallate, BHA, BHT and monothioglycerol from about 0.005 to 1.0% w/v and an additive at up to 50% v/v the additive being propylene glycol, Tween 80, Crodamol/CAP, Vitamine E, or glycerol formal.

20. A topical formulation for direct application to the skin of an animal for effective treatment of parasitic infestations consisting of 5.0% w/v of polyvinyl pyroolidone, molecular weight

45,000, 5.0% w/v of 22,23-dihydro-13-O-[(2-methoxyethoxy)methyl] avermectin B1 aglycone, 90% v/v ethanol q.s. to 100% with water and 0.01% w/v BHT.

21. A process for the preparation of the formulation of Claim 1 which comprises dissolving the avermectin compound in about 50% of the volume of the carrier and adding as a final volume, the remainder of the carrier.

22. The process of Claim 10 wherein the additional solvent and antioxidant may be combined with the carrier prior to mixing with the avermectin or added as the final volume of solvent or additive.

23. A process for the preparation of the formulation of claim 12 which comprises dissolving the avermectin compound in the alcohol to form a clear solution, adding and dissolving the anti-oxidant and polymeric material in the solution, adding the additive, adjusting the volume to 100% by addition of the water, and mixing until the solution is homogeneous.

24. A method for the treatment and prevention of internal and external parasites of animals, which comprises topically applying the formulation of Claim 1 to the skin of an animal.

25. A method for the treatment and prevention of internal and external parasites of animals, which comprises topically applying the formulation of Claim 12 to the skin of an animal.

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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHOI, Hoo-Kyun [KR/US]; 1280 McDivitt Drive, Blue Bell, PA 19422 (US). WILLIAMS, James, B. [US/US]; 2259 Warner Road, Lansdale, PA 19446 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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(54) Title: POUR-ON FORMULATIONS CONTAININNG POLYMERIC MATERIAL, GLYCOLS AND GLYCERIDES

(57) Abstract

There is disclosed a topical formulation containing glycols, glycerides, or their derivatives, an avermectin compound (active ingredient) and optionally a polymeric material which has been discovered to provide superior efficacy against endoparasites and ectoparasites when compared to conventional formulations and to maintain the concentration of the active compound in the milk of dairy animals below a safe concentration for human consumption. The formulation contains the avermectin active ingredient and at least 50 % of the glycol or glyceride or polymeric material.

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 94/04664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A01N43/90 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 120 286 (THE WELLCOME FOUNDATION LIMITED) 3 October 1984 see page 1, line 17 - page 3, line 20; claims; examples ---	1-11,21, 22,24
Y	EP,A,0 249 409 (COOPERS ANIMAL HEALTH LIMITED) 16 December 1987 see page 2, line 16 - page 3, line 15; claims ---	1-11,21, 22,24
Y	EP,A,0 051 786 (BAYER AG) 19 May 1982 see page 4, line 5 - page 5, line 11 see page 6, line 18 - page 7, line 19; claims; examples --- -/--	1-11,21, 22,24 12,13, 15-19, 23,25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 February 1995	02.03.95

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interr ·nal Application No
PCT/US 94/04664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 137 627 (ICI AUSTRALIA LIMITED) 17 April 1985 see page 5, line 11 - page 7, line 23 see page 8, line 22 - page 8, line 35 see page 11, line 6 - page 11, line 33; claims; examples	1-4,6-8, 24
X Y	EP,A,0 329 460 (AMERICAN CYANAMID COMPANY) 23 August 1989 see page 1, line 10 - page 2, line 9 see page 7, line 34 - page 7, line 50	1-4,6-9, 24 19
X	EP,A,0 432 494 (AMERICAN CYANAMID COMPANY) 19 June 1991 see page 3, line 1 - page 3, line 53; claims; examples	1-4,24
X	EP,A,0 045 655 (MERCK & CO. INC.) 10 February 1982 see the whole document	1-4,24
X	EP,A,0 146 414 (MERCK & CO. INC.) 26 June 1985 see page 2, line 19 - page 2, line 31; claims; examples	1-9,21, 24
A	EP,A,0 136 033 (ICI AUSTRALIA LIMITED) 3 April 1985	
Y	EP,A,0 193 347 (MERCK & CO. INC) 3 September 1986 see page 8 - page 9, line 22 see page 22, line 20 - line 28	12,13, 15,23,25
A	see page 26, line 15 - line 24; examples 3,6,33	14,20
Y	FR,A,2 599 220 (SOCIETE MEDITERRANEENNE D'AEROSOLS & J. JUNQUA) 4 December 1987 see page 1 - page 2, line 6 see page 3, line 22 - page 4, line 15	16-18

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US 94/04664

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. Claims: 1-11,21,22,24 as far as the carrier is a glycol, glyceride, or derivate thereof
2. Claims: 12-20,23,25 as far as the carrier is an alcohol/water mixture.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 94/04664

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